Glycaemic Control and Development of Retinopathy in Type 2 Diabetes Mellitus: A Longitudinal Study**

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Relationships between glycaemic control, hypertension, and development of microangiopathy have been well documented in Type 1 (insulin-dependent) but not in Type 2 (non-insulin-dependent) diabetes mellitus. Therefore, we have investigated these relationships in a cohort of 64 Type 2 patients free of retinopathy (by angiofluorography), who were regularly followed until development of retinopathy or for at least 7 years as outpatients. Glycaemic control was assessed by 1 to 4 HbA_1 determinations per year. Retinal status was monitored by annual angiofluorography. Nonproliferative retinopathy developed in 14 patients (cumulative incidence at 13 years: 29.8 %) after a mean diabetes duration of 14.3 ± 8.9 years (range 2–27). In multivariate analysis (Cox model), mean HbA_1 during follow-up ($p < 0.001$), and hypertension at first examination ($p = 0.09$) were associated with the development of retinopathy, but age, sex, BMI, diabetes duration, smoking, and fasting blood glucose were not. The relative risk for developing retinopathy (RR) was 7.2 (IC 95 %: 1.61–32.4) in patients with a mean HbA_1 during follow-up above the median value of the cohort (8.3 %) compared with patients with HbA_1 during follow-up below this value. RR was 2.5 (IC 0.8–8) in patients with HbA_1 at first examination above compared to below the median value (8.4 %). RR was 3.0 (IC 0.9–10) in patients treated for hypertension at baseline compared to those without treatment. A sixfold increase in retinopathy prevalence was observed between patients with mean HbA_1 in the highest or lowest quartile of mean HbA_1 distribution during follow-up. This longitudinal study indicates a strong association between long-term glycaemic control and the development of diabetic retinopathy in Type 2 diabetes. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Relationships between glycaemic control, hypertension, and development of retinopathy have been well documented in Type 1 (insulin-dependent) diabetes mellitus by epidemiological[1,2] as well as intervention studies.[3] However data concerning these relationships in Type 2 (non-insulin-dependent) diabetes mellitus are sparse.[4] Therefore, this study was aimed at investigating relations between long-term glycaemic control and development of retinopathy in a homogeneous cohort of Type 2 patients regularly followed in the same centre for 7 to 13 years and free of retinopathy at first examination.

Patients and Methods

Patients

We performed a retrospective analysis of the clinical records of all diabetic patients who had a fluorescein angiography at the Ophthalmological Department of Lariboisiere Hospital during 1993–94. We included in this retrospective prospective study all the patients who fulfilled all the following criteria:

1. Type 2 diabetes mellitus, defined according to WHO criteria,[5] without any history of ketoacidotic episodes, and no insulin treatment for at least 3 years after diagnosis.
2. Regular follow-up until development of retinopathy or for at least 7 years at the Diabetes and Ophthalmology Departments of Lariboisiere Hospital, with

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Table 1. Characteristics of patients at entry to study

	Mean (±SD)	Range
Age (years)	54.5 ± 9.1	31–79
Diabetes duration (years)	7.5 ± 6.9	0–24
BMI (kg m^{-2})	26.2 ± 4	16–38
Systolic blood pressure (mmHg)	143 ± 21	100–200
Diastolic blood pressure (mmHg)	85 ± 14	50–130
Serum creatinine (μmol l^{-1})	83 ± 14	50–120
Urinary albumin excretion (mg $24h^{-1}$)	11 ± 52	0–320
Fasting blood glucose (mmol l^{-1})	9.0 ± 2.3	5.2–17.2
HbA_1 (%)	8.6 ± 1.5	5.6–13

glycated haemoglobin (HbA_1) determinations and annual fluorescein angiography, performed on site.

3. Absence of diabetic retinopathy evidenced by fluorescein angiography at entry to the study.

Entry to the study is defined by the first ophthalmological examination without retinopathy in our centre. At that time, diabetes duration was 7.5 ± 6.9 (0–24) years (Tables 1 and 2). A total of 64 patients with a first examination between 1979 (date of introduction of HbA_1 assay) and 1986 (Table 1) met these criteria. We collected data from the records from the initial HbA_1 determination until 1993–94. At the beginning of the study, 10 patients were treated with diet, 53 with diet and oral hypoglycaemic agents (19 with sulphonylureas, 12 with metformin, and 22 with both). Only 1 patient was insulin-requiring (after 8 years of treatment with oral hypoglycaemic agents). At the end of follow-up, 1 patient was treated with diet, 48 with diet and oral hypoglycaemic agents (11 with sulphonylurea, 3 with metformin, and 34 with both). Fifteen patients were treated with insulin. Non-smokers ($n = 39$) were defined as patients who had never smoked or who had smoked less than 5 pack-years. Blood pressure was measured after a 5-min rest in the supine position. Hypertension (33 cases) was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg (23 cases), and/or treatment for hypertension (10 cases) (β-blockers or diuretics). Four patients were on long-term antiplatelet therapy.

Methods

Glycaemic control was evaluated during follow-up by fasting blood glucose and HbA_1 determinations. In the analysis, two different measures of HbA_1 were used: study entry HbA_1 (mean of all HbA_1 determinations performed during the calendar year of entry into the study) and mean HbA_1 during follow-up (mean of all HbA_1 determinations during follow-up). Blood glucose was assayed by the glucose dehydrogenase method on venous plasma. Total HbA_1 was measured by the microcolumn method (Lab Biorad, Paris, France) with temperature control as previously described.[6] Intra- and inter-assay coefficients of variation based on 30 replicates were 4.3 % and 5.3 %, respectively. The non-diabetic range for HbA_1 (mean ± 2 SD) was 6.1 ± 2.4 % established in 53 control subjects with a normal 75 g OGTT according to WHO.[5] Ophthalmological evaluation was performed annually. Fluorescein angiographies were

Table 2. Characteristics and significant differences between patients with and without development of retinopathy during follow-up

	Retinopathy at follow-up	No retinopathy at follow-up	*p* value
n	14	50	
Sex (M/F)	7/7	28/22	NS
Total follow-up duration (years)	11.5 (7–14)	10 (7–14)	
Diabetes duration (years) (at baseline)	3.5 (0–24)	6 (0–21)	NS
BMI (kg m^{-2})	26 (23–32)	25 (16–38)	NS
Systolic blood pressure (mmHg)	140 (120–180)	140 (100–200)	NS
Diastolic blood pressure (mmHg)	90 (70–130)	80 (50–120)	NS
Serum creatinine (μmol l^{-1})	90 (60–120)	80 (50–120)	NS
Fasting blood glucose (mmol l^{-1}) (at baseline)	9.4 (5.6–13.7)	8.6 (5.2–17.2)	NS
HbA_1 (%) (at baseline)	9.7 (6.8–11.1)	8.2 (5.6–13)	< 0.03
HbA_1 (%) (mean during follow-up)	9.1 (6.1–11.1)	8.1 (6.1–11.2)	< 0.03
Hypertension (%) (at baseline)	43	34	NS
Treatment for hypertension (%) (at baseline)	28.6	12	NS
History of smoking (%)	38	43	NS
Urinary albumin excretion ≥ 30 mg $24\ h^{-1}$ (%)	8	4	NS

Data are expressed as median (range in brackets).

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read by two independent observers trained in diabetic ophthalmology who were blind to patient identity and to each other evaluation.

Statistical Analysis

Data are expressed as means ± SD. Univariate comparisons were done by Wilcoxon and chi-square tests. Cumulative incidence of retinopathy was computed by actuarial survival analysis and comparisons between groups used the log-Rank test. A multivariate analysis of predictors of retinopathy was performed with Cox's proportional hazards model.

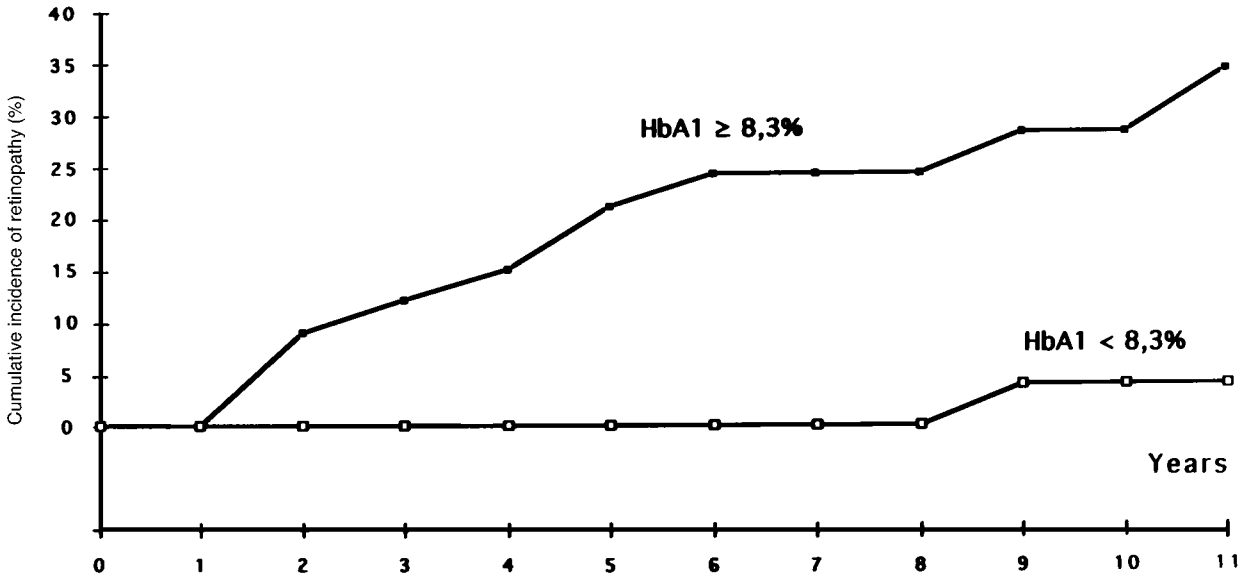
Results

By the end of the period of observation, 14 patients (30 %) had developed a background retinopathy, with a 13-year cumulative incidence of 29.8 % (Table 2). The retinopathy was first detected after a mean follow-up of 4.5 (range 1–13) years and after a mean known diabetes duration of 14.3 ± 8.9 (range 2–27) years. Retinopathy was mild (microaneurysms only) and unilateral in 4 cases. At the end of follow-up (7–14 years) no proliferative retinopathy had been observed. Retinopathy remained mild in 8 patients and worsened in the 6 others (moderate or moderately severe non-proliferative diabetic retinopathy). HbA_1 at entry to the study and during follow-up was higher in patients who developed retinopathy when compared with patients without retinopathy (Table 2). In univariate survival analysis, the cumulative incidence of retinopathy was not significantly different in patients with study entry HbA_1 above the median value of the cohort (8.4 %) compared with patients with study entry HbA_1 below this median value ($p = 0.11$). A significantly increased cumulative incidence of retinopathy was observed in patients with a mean HbA_1 during follow-up above the median value (8.3 %) compared with patients with a mean HbA_1 during follow-up below this median value ($p = 0.002$; Figure 1). There was a trend ($p = 0.06$) toward an increase in cumulative incidence of retinopathy in patients who were treated for hypertension in study entry compared with those without treatment (Figure 2). Relative risks for development of retinopathy are given in Table 3. Multivariate analysis according to Cox's model was performed to test the independence of parameters with a p value less than 0.10 in univariate analysis. Mean HbA_1 during follow-up ($p < 0.001$) and treatment for hypertension at study entry ($p = 0.09$) were independently associated with the development of retinopathy. We determined the prevalence of retinopathy according to the quartiles of the distribution of mean HbA_1 during follow-up. A sixfold increase was observed between the lowest (6.25 %) and the highest quartile (39 %, $p < 0.01$) of the distribution of mean HbA_1 during follow-up.

Discussion

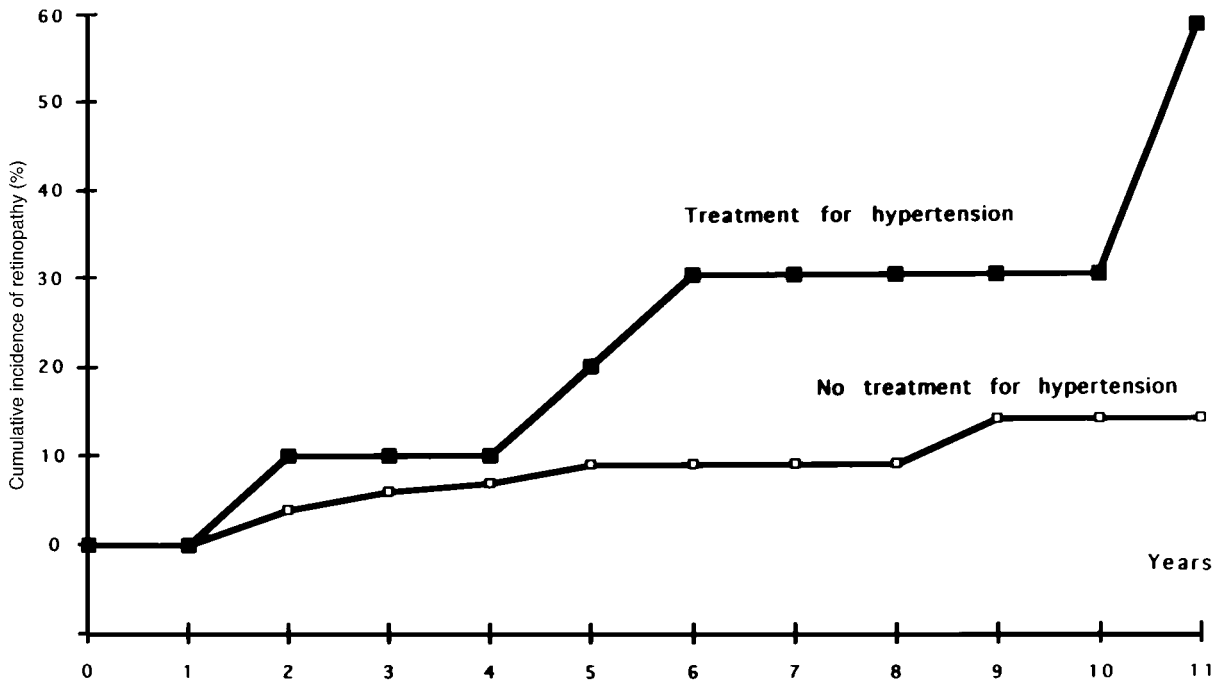
In a homogeneous cohort of 64 Type 2 diabetic patients followed for a mean of 10 years, new background retinopathy developed in 14 cases. Mean HbA_1 at study entry and during follow-up was higher in patients who developed retinopathy. Since the introduction in clinical practice of HbA_1 (or HbA_{1C}) assay, a reliable marker of long-term glycaemic control,[7] longitudinal studies have shown that in Type 1 diabetic patients, glycaemic control and diabetes duration are the most prominent determinants of retinopathy.[1,2,8] However, data are sparse in Type 2 subjects. Cross-sectional studies have shown that diabetes duration[9–12] and HbA_1[9–11,13,14] are associated with the presence of retinopathy. In prospective longitudinal studies the association between baseline HbA_1 (or HbA_{1C}) and subsequent development of retinopathy has been observed in Pima Indians[13] and in patients with diabetes onset after 30 years of age, taking insulin or not.[14] In the Wisconsin study, HbA_{1C} was determined at baseline and at the 4-year follow-up examination.[14] The changes between the two values of HbA_{1C} were associated with progression of retinopathy over 10 years. In our study, glycaemic control was evaluated by assaying HbA_1 at study entry and regularly during follow-up (1–4 determinations per year). In multivariate analysis, only HbA_1 during follow-up was independently associated with the development of retinopathy. In contrast to earlier reports, HbA_1 at diagnosis was not predictive of retinopathy later.[13,15]

No relation was observed between diabetes duration and retinopathy development, in contrast with reports of other groups.[9–12] However, diabetes duration in Type 2 disease is a non-reliable parameter, as the diabetes may remain undiagnosed for years in many cases.[16] Furthermore, our study design will have only included patients who either presented early in the course of their disease or had survived up to 2 years (the extreme case) without retinopathy, which may have introduced a bias towards lower risk patients. In some of our patients, retinopathy developed in spite of good metabolic control. We cannot exclude the influence of previous poor glycaemic control, as suggested by studies in experimental diabetes.[17] Finally treatment for hypertension and development of retinopathy were only weakly associated in univariate analysis. This issue remains controversial, with the presence of a relationship in some studies[10,11,18] and its absence in others.[19,20] Intensive treatment with insulin has been shown to be effective in delaying the onset and progression of retinopathy in Type 1 diabetes[3] and in a particular subgroup of non-obese insulin-requiring Japanese Type 2 patients.[21] Our study indicates, in the more common form of mildly obese patients with non-insulin-requiring Type 2 diabetic disease, there is also a strong association between long-term glycaemic control and the development of retinopathy.



	Years	0 - 1	- 2	- 3	- 4	- 5	- 6	- 7	- 8	- 9	- 10	- 11
HbA1 < 8,3	Subjects at risk (n)	31	31	31	31	31	31	31	31	26	20	16
	cases (n)	0	0	0	0	0	0	0	0	1	0	0
HbA1 ≥ 8,3	Subjects at risk (n)	33	33	30	29	28	26	25	24	21	16	13
	cases (n)	0	3	1	1	2	1	0	0	1	0	1

Figure 1. Relationship of development of retinopathy and glycaemic control: cumulative incidence of retinopathy according to mean HbA_1 during follow-up: ■——■ patients with HbA_1 above median value (8.3 %); □——□ patients with HbA_1 below median value ($p = 0.002$, log rank test)



Treatment	Years	0 - 1	- 2	- 3	- 4	- 5	- 6	- 7	- 8	- 9	- 10	- 11
No	Subjects at risk (n)	54	54	52	51	50	49	49	48	41	32	26
	cases (n)	0	2	1	1	1	0	0	0	2	0	0
Yes	Subjects at risk (n)	10	10	9	9	9	8	7	7	6	4	3
	cases (n)	0	1	0	0	1	1	0	0	0	0	1

Figure 2. Relationship of development of retinopathy and treatment of hypertension: cumulative incidence of retinopathy according to the presence ■——■ or the absence □——□ of treatment for hypertension at baseline ($p = 0.06$, log rank test)

Table 3. Relative risk of retinopathy during follow-up according to HbA_1 at baseline, mean annual HbA_1 during follow-up, and treatment for hypertension at baseline in separate univariate analysis

	Relative risk	Confidence interval 95 %
HbA_1 at baseline $\geq$ 8.4 %	2.5	0.8–8
Mean HbA_1 during follow-up $\geq$ 8.3 %	7.2	1.61–32.4
Treatment for hypertension at baseline	3	0.9–10

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